PBE-based model for a complex problem: solid-state deracemisation

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Outline

- Introduction on chirality
- Chiral resolution and solid-state deracemisation
- Viedma Ripening and temperature cycles: experimental evidence
- Viedma Ripening and temperature cycles: modeling approach
  - The PBE model
  - Simulation results
- What do we do at SPL?
What’s chirality?

- An object (e.g. a molecule) is chiral if it is non-superimposable with its mirror image
- This object is called enantiomer
Motivation

In achiral environments
- same physical properties (melting point, etc.)

In chiral environments (e.g. human body)
- very different properties
- often important to select one enantiomer
Optical activity

Chiral molecules in solution rotate the direction of a linearly polarized beam

Dextrorotatory, d, (+)  
clockwise rotation
Levorotatory, l, (-)  
counter clockwise rotation

\[ ee_i = \frac{\alpha_M}{\alpha_i} \]

\[ ee_i = \frac{m_i - m_{j \neq i}}{m_i + m_{j \neq i}} \]
Chiral center: terminology

**Fisher-Rosanoff convention**

\[
\begin{align*}
\text{d-glyceraldehyde} & \quad \text{CHO} \quad \text{H} \quad \text{OH} \quad \text{CH}_2\text{OH} \\
\text{l-glyceraldehyde} & \quad \text{HO} \quad \text{H} \quad \text{CHO} \quad \text{CH}_2\text{OH}
\end{align*}
\]

**Absolute configuration**

Cahn-Ingold-Prelog, 1966
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Chiral resolution

- Separation of the racemate (equimolar mixture) into its pure enantiomers.

Chromatography
- Single column chromatography
- Multicolumn continuous chromatography

Crystallization
- Diastereomeric resolution
- Preferential crystallization
- Solid-state deracemisation
Chiral resolution

- Separation of the racemate (equimolar mixture) into its pure enantiomers.

Isolation of enantiopure crystals, starting from a suspended mixture of the two enantiomers

- Viedma-ripening (attrition-enhanced)
- Deracemisation via temperature cycles

Crystallization

- Diastereomeric resolution
- Preferential crystallization
- Solid-state deracemisation
Solid-state deracemisation

- **Strengths**
  100% enantiopure product
  > 50% yield

- **Weaknesses**
  Many phenomena involved
  Restricted application: conglomerate compound, racemizable

\[ k_1 = k_{-1} = k \]

Pseudo-first-order rate constant [min\(^{-1}\)]

**Rate equation**

\[ \frac{d [ee]}{dt} = -2k_{ee} \]

**DBU: basic catalysis**

\[ k = k_0 + k_B c_B \]

1\(^{st}\)-order rate constant for the uncatalysed reaction [min\(^{-1}\)]. Ass. \( k_0 = 0 \)

2\(^{nd}\)-order rate constant for the base catalised reaction [min\(^{-1}\)M\(^{-1}\)]

**Temperature dependence**

\[ k_B = \frac{k}{c_B} = A_0 e^{-\frac{E_a}{RT}} \]
Conglomerate compound

Crystallisation

Racemic compound

Equal amounts of the two enantiomers in a well defined arrangement within the crystal lattice

Conglomerate compound

An equimolar mechanical mixture of crystals each one of which contains only one of the two enantiomers

Solid solution

Different amounts of the two enantiomers in the crystal lattice
Conglomerate compound

Crystallisation

Racemic compound

Conglomerate compound

Solid solution
Ternary phase diagram

Example: Conglomerate compound
Conglomerate compound

Crystallisation

Racemic compound

Conglomerate compound

Solid solution
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Solid-state deracemisation

• **Viedma ripening**
  A suspension of the two enantiomers is stirred in the presence of glass beads

  Dissolution and growth thanks to *size-dependent solubility*

• **Temperature cycles**
  A suspension of the two enantiomers is undergoes periodic temperature variation

  Dissolution and growth thanks to *temperature oscillation*
Viedma Ripening: experimental results

Introducing an initial asymmetry allows to drive the resolution toward the desired enantiomer.

\[ e \varepsilon_i = \frac{m_i - m_{j \neq i}}{m_i + m_{j \neq i}} \]

An undetectable initial asymmetry can result in an apparent erratic behaviour.


Viedma Ripening: effect of the initial conditions

Simulating the introduction of small initial asymmetries shows the non-stochastic nature of the outcome.

The variability decreases, when a large asymmetry is introduced.

Solid-state deracemisation

- **Viedma ripening**
  A suspension of the two enantiomers is stirred in the presence of glass beads.

Dissolution and growth thanks to *size-dependent solubility*

- **Temperature cycles**
  A suspension of the two enantiomers is undergoes periodic temperature variation.

Dissolution and growth thanks to *temperature oscillation*
Temperature cycles

Temperature cycles (T°C) versus time (t [min])

- A: Temperature minimum ($T_{\text{min}} = 26°C$)
- B: Maximum temperature ($T_{\text{MAX}} = 38°C$)
- C: Return to starting temperature
- D: End of cycle

Energy content (c [kJ/kg]) versus temperature (T [°C])

- A: Starting point
- C: End point of temperature cycle
- B: End point of energy content cycle
- D: Intermediate point
Temperature cycles: process monitoring

Monitoring the solid-phase ee over time: a small suspension sample is taken just before point A, filtered, washed, and re-dissolved for chiral HPLC analysis.
Temperature cycles: experimental protocol

- 1,5-diazabiciclo[5.4.0]undec-5-ene (3.85 μL/g)
- Isopropanol:Acetonitrile (95:5 w/w)

<table>
<thead>
<tr>
<th>Suspension density [w%]</th>
<th>2.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heating rate [°C/min]</td>
<td>1.30</td>
</tr>
<tr>
<td>Crystalliser volume [mL]</td>
<td>1.8</td>
</tr>
<tr>
<td>Fraction of suspended solid dissolved</td>
<td>30%</td>
</tr>
<tr>
<td>ee₀ [%]</td>
<td>7, 18, 32/36, 50</td>
</tr>
<tr>
<td>Cooling rate [°C/min]</td>
<td>1.30, 0.43, 0.22, 0.14</td>
</tr>
<tr>
<td>T_min [°C]</td>
<td>20, 25, 30</td>
</tr>
</tbody>
</table>

\[ Δc = c^* (T_{\text{MAX}}) - c^* (T_{\text{MIN}}) \]

The initial enantiomeric excess

The process occurs faster when increasing the initial enantiomeric excess. The absolute process time depends on the specific system.

NMPA

- Initial enantiomeric excess: 7%, 18%, 32%
- $T_{\text{min}} = 25 \, ^\circ\text{C}$
- $T_{\text{MAX}} = 38 \, ^\circ\text{C}$
- $R_c = 0.22^\circ\text{C}$

CPG

- Initial enantiomeric excess: 50%, 36%, 20%
- $T_{\text{min}} = 25 \, ^\circ\text{C}$
- $T_{\text{MAX}} = 37 \, ^\circ\text{C}$
- $R_c = 0.22^\circ\text{C}$
The cooling rate: NMPA

Increasing the cooling rate speeds up deracemisation in the time domain, but it slows it down in term of number of cycle.

\[ t_{\text{tot}} = n_c \cdot t_{\text{cycle}} \]
Viedma ripening and deracemisation via temperature cycles are different processes, but they are characterised by similar features.

From experimental data, it has been shown that:

- an initial enantiomeric excess drives the resolution toward the desired enantiomer, and shortens the process time.

- more operating parameters can be tuned in the case of temperature cycles.

- the process time is system-specific

- How can we model such complex processes?
- Can the model help us in gaining a better understanding?
- Can we confirm the trends observed experimentally by simulating the solid-state deracemisation?
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